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Global Cortical Atrophy Is Associated with an Unfavorable Outcome in Stroke Patients on Oral Anticoagulation

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Keywords
Small vessel disease · Stroke · Global cortical atrophy · Intracerebral hemorrhage · Atrial fibrillation

Abstract
Introduction: Measures of cerebral small vessel disease (cSVD), such as white matter hyperintensities (WMH) and cerebral microbleeds (CMB), are associated with an unfavorable clinical course in stroke patients on oral anticoagulation (OAC) for atrial fibrillation (AF). Here, we investigated whether similar findings can be observed for global cortical atrophy (GCA). ***Methods:*** Registry-based prospective observational study of 320 patients treated with OAC following AF stroke. Patients underwent magnetic resonance imaging (MRI) allowing assessment of GCA. Using the simplified visual Pasquier scale, the severity of GCA was categorized as follows: 0: no atrophy, 1: mild atrophy; 2: moderate atrophy, and 3: severe atrophy. Using adjusted logistic and Cox regression analysis, we investigated the association of GCA using a composite outcome measure, comprising: (i) recurrent acute ischemic stroke (IS); (ii) intracranial hemorrhage (ICH); and (iii) death. ***Results:*** In our time to event analysis after adjusting for potential confounders (i.e., WMH, CMB, age, sex, diabetes, arterial hypertension, coronary heart disease, hyperlipidemia, and antiplatelet use), GCA was associated with an increased risk for the composite outcome in all three degrees of atrophy (grade 1: aHR 3.95, 95% CI 1.34–11.63, $p = 0.013$; grade 2: aHR 3.89, 95% CI 1.23–12.30, $p = 0.021$; grade 3: aHR 4.16, 95% CI 1.17–14.84, $p = 0.028$). ***Conclusion:*** GCA was associated with our composite outcome also after adjusting for other cSVD markers (i.e., CMB, WMH) and age, indicating that GCA may potentially serve as a prognostic marker for stroke patients with atrial fibrillation on oral anticoagulation.

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Introduction

Nonvalvular atrial fibrillation (AF) is a common cause of acute ischemic stroke (IS) and oral anticoagulation (OAC) is the treatment of choice for secondary prevention of recurrent IS [1–4]. Direct oral anticoagulants (DOACs) are commonly used as the standard of care in AF stroke [5, 6] given their more favorable safety profile with regard to the risk of intracranial hemorrhage (ICH) [7, 8].

Given that cerebral small vessel disease (cSVD) is an age-related condition similar to AF, it is often found in patients with AF-related ischemic stroke. cSVD and AF share common risk factors such as arterial hypertension and diabetes. In addition, cSVD is another important cause of stroke and the most common underlying vascular condition leading to ICH [9–11].

We and others have recently shown that magnetic resonance imaging (MRI) measures associated with cSVD are related to a more unfavorable clinical course in stroke patients on antithrombotic treatment – including OAC – for secondary stroke prevention [12–15]. These MRI measures included white matter hyperintensities (WMH) and especially cerebral microbleeds (CMBs), which were associated with an increased risk of both, recurrent IS and ICH. Furthermore, as known for neurodegenerative diseases such as Alzheimer's disease, cSVD is known to eventually lead to brain atrophy [16–19]. However – in contrast to WMH and CMBs – little is known on global cortical atrophy (GCA) in patients taking OAC for AF. Taking into consideration that cSVD is a risk factor for both – ischemic and hemorrhagic stroke – the risk assessment for these outcomes is especially relevant for patients with AF under OAC. This patient population has an elevated risk of recurrent stroke; however under OAC severe ICH may occur in clinical practice. Thus, an individualized risk assessment in this patient cohort based on easily assessable imaging measures is of clinical interest. The aim of the present observational, prospective cohort study was to explore the potential impact of GCA on the clinical course and outcome in AF patients treated with oral anticoagulants – predominantly DOACs – after IS or transient ischemic attack (TIA).

Methods

Study Design and Patient Cohort

We based our study on stroke patients under OAC included in the prospective registry named NOACISP-Longterm (Novel Oral Anticoagulants in Ischemic Stroke Patients; NCT03826927) carried out at the stroke center of the University Hospital of Basel. Adult patients (>18 years) with AF treated with DOACs or vitamin K antagonists (VKA) after an IS or TIA were enrolled since April 2013 as reported previously [12]. The diagnosis of AF during hospitalization was based on a 12-lead ECG or a long-term monitoring device. The patient had a standardized follow-up with an inpatient visit at 3 months and thereafter regular telephone interviews at 6 and 12 months with a final call 24 months after the index stroke. During these visits, clinical data on outcome events as defined below, adverse events, and medical adherence were collected. For this study, we included patients treated at our stroke center up to August 2016 with available MRI of the brain and at least a 3-month follow-up visit. We excluded 5 patients primarily treated with antiplatelet therapy.

Neuroimaging Analysis

As described previously [12], MRI was performed using a standardized stroke protocol including axial DWI and apparent diffusion coefficient, axial T2-weighted/or fluid-attenuated inversion recovery imaging and susceptibility-weighted imaging with whole-brain coverage. We categorized MRI quality as good, sufficient with little artifacts and insufficient. Patients with insufficient imaging quality were excluded from this study.

The evaluation of GCA was based on axial T1 sequences and if not available on fluid-attenuated inversion recovery sequences. We used the simplified – and previously used [20, 21] – visual Pasquier scale that categorizes the severity of GCA as follows: 0 – no atrophy (normal brain volume, no sulcal widening); 1 – mild atrophy (opening of sulci, early peripheral widening); 2 – moderate atrophy (gyral volume loss, diffuse widening of sulci); and 3 – severe atrophy (severe gyral thinning, knife-edge appearance). In 2 patients, the quality of the needed MRI sequences was insufficient to allow a visual rating of the degree of GCA. The assessment of CMB and WMH was described previously [12]. In 4 patients the degree of white matter hyperintensities could not be assessed.

Three experienced readers (M.K., A.Z., N.P.) conducted the assessments. After consensus reading for the first 10% of the images, the assessments were performed blinded to the clinical outcome with consensus reading for ambiguous cases.

Study Outcomes

The primary outcome was the composite of (i) recurrent IS (i.e., acute focal neurological deficit >24 h with corresponding lesions on DWI, or, if no MRI was acquired, signs of early ischemic injury on CT); (ii) ICH (i.e., clinically manifest bleeding visible on CT or MRI in accordance to the ISTH criteria [22]); and (iii) all-cause death. In addition, the distribution hazard for each of these outcome parameters was also analyzed. Finally, we analyzed functional outcome measured by the modified Rankin scale (mRS) at 3 months as part of a clinical in person visit and at 6, 12, and 24 months via telephone interviews.

Statistical Analyses

Using descriptive statistics, we analyzed the clinical and neuroimaging markers. We grouped our patients regarding the presence and degree of the overall GCA.

We used the χ^2 test to compare the categorical variables, the numbers and proportions are presented accordingly. For continuous variables, mean and standard deviations were calculated, and the *t* test was used to compare the above-mentioned groups. We

Table 1. Patient characteristics by the presence of global cortical atrophy

	Overall cohort	No atrophy	Mild atrophy	Moderate atrophy	Severe atrophy	*p* value[†]
Demographics						
Patients, *N*	313	63	139	79	32	
Age, years, mean (SD)	78.1 (9.2)	68.9 (10.5)	78.4 (7.1)	82.4 (6.6)	84.2 (6.0)	<0.001
Male sex, *n* (%)	170 (54.3)	42 (66.7)	71 (51.1)	40 (50.6)	17 (53.1)	0.179
Qualifying event, *n* (%)						
TIA	31 (9.9)	9 (14.3)	10 (7.2)	10 (12.7)	2 (6.2)	0.302
Medication, *n* (%)						
DOAC	217 (69.3)	48 (76.2)	98 (70.5)	49 (62)	22 (68.8)	0.262
DOAC/antiplatelet	18 (5.8)	6 (9.5)	6 (4.3)	4 (5.1)	2 (6.2)	
VKA	62 (19.8)	6 (9.5)	26 (18.7)	23 (29.1)	7 (21.9)	
VKA/antiplatelet	16 (5.1)	3 (4.8)	9 (6.5)	3 (3.8)	1 (3.1)	
No concomitant antiplatelet use, *n* (%)	279 (89.1)	54 (85.7)	124 (89.2)	72 (91.1)	29 (90.6)	0.762
Vascular risk factors, *n* (%)						
Hypertension	238 (76)	44 (69.8)	105 (75.5)	65 (82.3)	24 (75.0)	0.383
Diabetes	62 (19.8)	11 (17.5)	25 (18)	15 (19)	11 (34.4)	0.186
Hypercholesterolemia	121 (38.7)	26 (41.3)	54 (38.8)	31 (39.2)	10 (31.2)	0.817
Non-smoking	237 (75.7)	47 (74.6)	108 (77.7)	59 (74.7)	23 (71.9)	0.892
No regular alcohol consumption	241 (77)	48 (76.2)	108 (77.7)	61 (77.2)	24 (75.0)	0.999
CHA2DS2-VASc score, median [IQR]	6.0 [5.0, 6.0]	4.0 [3.0, 6.0]	6.0 [5.0, 6.0]	6.0 [5.0, 6.5]	6.0 [5.0, 6.0]	<0.001
HAS-BLED score, median [IQR]	2.0 [2.0, 3.0]	2.0 [1.0, 3.0]	2.0 [2.0, 3.0]	2.0 [2.0, 3.0]	2.5 [2.0, 3.0]	0.002
WMH-ARMC, *n* (%)						
0: no lesion	16 (5)	8 (12.9)	7 (5.1)	0 (0.0)	1 (3.1)	<0.001
1: focal lesions	180 (58.3)	43 (69.4)	87 (63)	42 (54.5)	8 (25.0)	
2: incipient confluent lesions	98 (31.7)	10 (16.1)	42 (30.4)	28 (36.4)	18 (56.2)	
3: diffuse confluent lesions	15 (4.9)	1 (1.6)	2 (1.4)	7 (9.1)	5 (15.6)	
≥ 1 CMB, *n* (%)	85 (27.5)	16 (25.8)	30 (21.7)	27 (35.1)	12 (37.5)	0.102
Concomitant statin use, *n* (%)	239 (76.36)	51 (81)	107 (77)	58 (73.4)	23 (71.9)	0.682

SD, standard deviation; IQR, interquartile range; WMH, white matter hyperintensities; CMB, cerebral microbleeds; DOAC, direct oral anticoagulants; VKA, vitamin K antagonist; TIA, transient ischemic attack. [†] The *p* value refers to the differences of baseline characteristics between patients with and without GCA.

used the Mann-Whitney U test or the Kruskal-Wallis rank sum test in cases of violation of the normal distribution assumption.

To investigate the association between neuroimaging markers and the clinical outcome, we used two approaches: first, we analyzed the incidence of the outcome events in a mixed-effects logistics model, and the chosen predictor was the presence and the degree of the GCA. In a second step, we performed time to event analysis in a Cox proportional hazards model. In case of multiple outcome events, only the first event was regarded. In both models, we included sex, age, vascular risk factors (i.e., arterial hypertension, diabetes, hyperlipidemia, and coronary heart disease), and concomitant medication (i.e., concomitant antiplatelet use) as fixed effects. In the second step, we adjusted for other neuroimaging markers of cSVD such as WMH and CMB. These variables were determined apriori based on previous research [12]. In addition, we used a subdistribution regression hazard model based on Fine-Gray for the competing events IS, ICH, and all-cause death. However, in these models, no covariate adjustment was performed, due to the small number of events.

The association with the functional outcome based on the mRS at 3, 6, 12, and 24 months during follow-up was assessed with a mixed-effects proportional odds model (i.e., ordinal logistic regression model; "shift-analysis"). The estimate of this model (common OR) indicates if atrophy is associated with higher odds for increased mRS. The proportional odds assumption was assessed graphically and in goodness-of-fit tests. Here the above-mentioned covariates (i.e., age, sex, arterial hypertension, diabetes, hyperlipidemia, and coronary heart disease) were included, as well as NIHSS at baseline reflecting the severity of the index stroke. As previously described, the analysis followed the STROBE criteria for observational studies [12, 23].

Results

The details on the cohort have previously been published [12]. In brief, the overall cohort comprised 320 patients. After excluding 5 patients primarily treated with antiplatelet therapy and 2 patients in which GCA could not be assessed, we evaluated 313 patients in total (see online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000527739). Median follow-up was 756 (IQR 712, 825) days, during which there

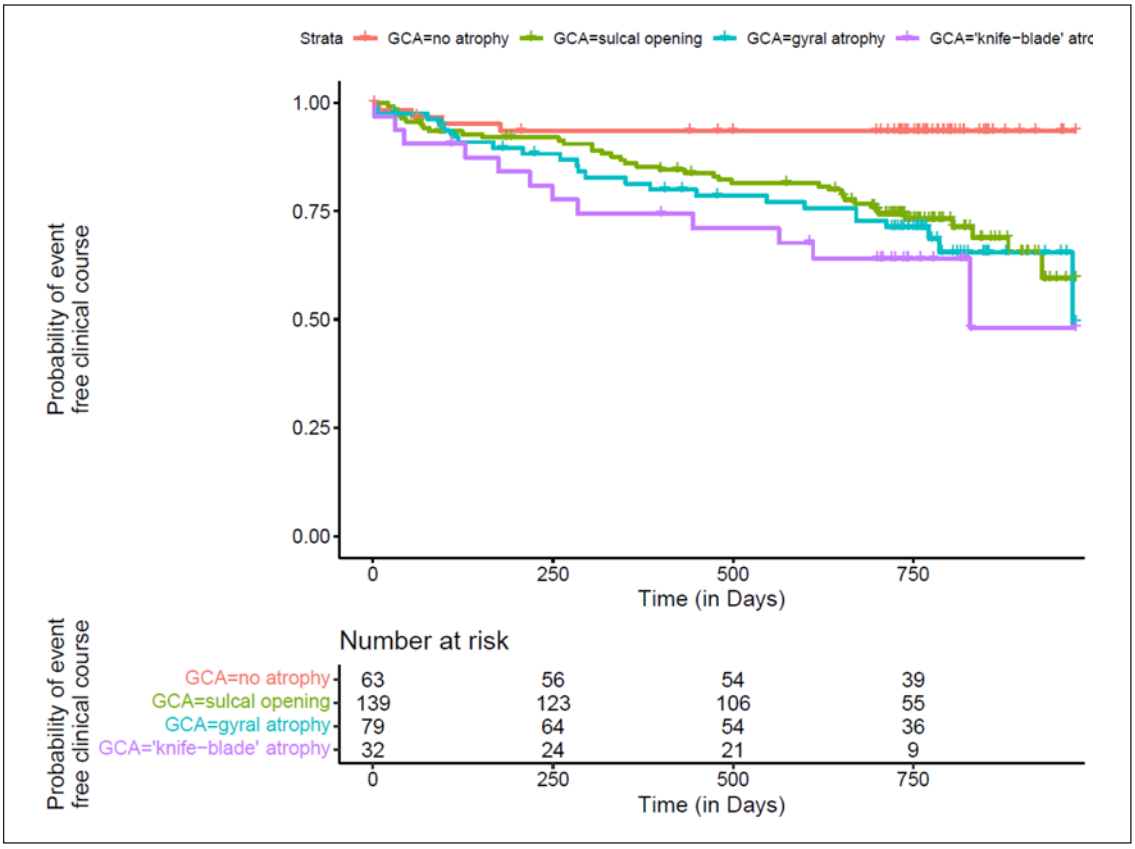

Fig. 1. Kaplan-Meier curve for the composite outcome by the degree of GCA. The patients are represented in different colors: red, patients with no atrophy (grade 0); green, mild atrophy (1); blue, moderate atrophy (2); and purple, severe atrophy (3).

Table 2. Association between GCA and the composite outcome compared to patients without GCA

	Adjusted OR* (95% CI)	*p* value	Fully adjusted OR† (95% CI)	*p* value
Mild atrophy (grade 1)	3.72 (1.38, 10.05)	0.009	3.50 (1.29, 9.56)	0.014
Moderate atrophy (grade 2)	4.30 (1.47, 12.51)	0.007	3.37 (1.14, 9.98)	0.028
Severe atrophy (grade 3)	4.59 (1.42, 14.85)	0.011	3.43 (1.03, 11.38)	0.044

CI, confidence interval; OR, odds ratio. * Adjusted for age, sex, arterial hypertension, diabetes, hyperlipidemia, coronary heart disease, and antiplatelet use. † Further adjusted for white matter hyperintensities and cerebral microbleeds.

were 23 recurrent IS, 7 ICH, and 51 patients died. The median time between the acquisition of the MRI and the qualifying event was 1 day (IQR 1, 2).

Demographic details of the patients with analysis of GCA are presented in Table 1. As expected, the degree of GCA increased with age. Furthermore, the presence of WMH and higher CHA2DS2-VASc and HASBLED scores were significantly more common in patients with GCA. CMBs were not associated with GCA.

In our mixed-effects logistic model, GCA was associated with an increased risk for the composite outcome in all three degrees of atrophy (grade 1: aOR 3.50, 95% CI 1.29–9.56, $p = 0.014$; grade 2: aOR 3.37, 95% CI 1.14–9.98, $p = 0.028$; grade 3: aOR 3.43, 95% CI 1.03–11.38, $p =$

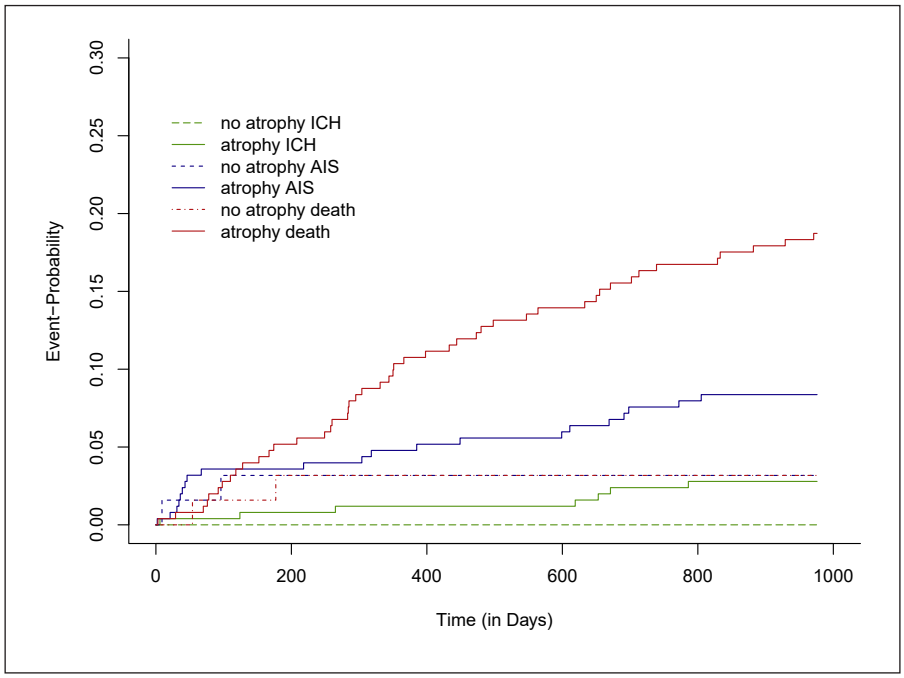

Fig. 2. Cumulative incidence functions for the association of GCA with the separate outcome measures (binary analysis: no atrophy vs. atrophy grade I-III). All ICH occurred in subjects with GCA (full green line) and GCA is associated with an increased risk of death (full red line). Death as an outcome parameter is illustrated in red, AIS in purple, and intracranial hemorrhage (ICH) in green.

0.044), after adjustment for age, sex, cardiovascular risk factors (i.e., diabetes mellitus, arterial hypertension, hyperlipidemia, coronary artery disease), and concomitant antiplatelet use and cSVD markers including WMH and CMBs (Table 2).

In the fully adjusted time to event analysis, the hazard ratio for the composite outcome was significantly elevated in patients with GCA as illustrated in Figure 1 (grade 1: aHR 3.95, 95% CI 1.34–11.63, $p = 0.013$; grade 2: aHR 3.89, 95% CI 1.23–12.30, $p = 0.021$; grade 3: aHR 4.16, 95% CI 1.17–14.84, $p = 0.028$).

Regarding the separate outcome events in our dichotomized analysis (brain atrophy grades 1–3 vs. no brain atrophy), all 7 cases of ICH occurred in patients with the presence of GCA ($p < 0.01$). Death was more frequent in patients with GCA (HR 6.38,95% CI 1.52–26.78, $p = 0.011$), whereas the association with IS was not significant (HR 2.69, 95% CI 0.62–11.61, $p = 0.19$). Figure 2 illustrates the findings for the separate outcome measures.

Moderate (grade 2) and severe (grade 3) GCA was associated with an unfavorable functional outcome based on the mRS in the adjusted analysis, including age, sex, arterial hypertension, diabetes, hyperlipidemia, coronary heart disease, and baseline stroke severity based on the NIHSS (grade 2: aOR 3.03, 95% CI 1.12–8.25, $p = 0.030$; grade 3: 4.11; 95% CI 1.19–14.20, $p = 0.026$). When also adjusting for imaging markers of cSVD (CMB, WMH), this association was not significant (online suppl. Table 1).

Discussion

In our study, the presence of GCA was associated with our composite outcome, comprising recurrent IS, ICH, and death. Regarding our outcome events separately, GCA was associated with death and ICH, but not IS in the univariate analysis.

Compared to the impact of CMB on the clinical course, as previously reported, even mild cortical atrophy had a slightly higher risk for the composite outcome than the presence of >1 CMB alone (aOR 3.50 vs. aOR 2.05) [12]. GCA is easily assessable and may thus be a helpful measure for prognostication in stroke patients under OAC for secondary prevention. Furthermore, GCA can potentially also be assessed on computed tomography not allowing detailed analyses of other cSVD-related markers such as CMBs.

The GCA rating scale has been used in the context of dementia [21] but also in a recent study from the CROMIS-2 cohort. Here, the authors identified a higher load of more than 10 enlarged perivascular spaces (PVS) within the basal ganglia – but not in the centrum semiovale – as a potential risk factor for spontaneous ICH in patients with recent AF-related stroke under OAC [20]. Taking into consideration that enlarged PVS could be a result of brain atrophy through reduction of cerebral parenchyma with secondary dilatation, the authors also studied GCA but found no association with ICH in that study [20].

In contrast to our study, CROMIS-2, however, did not include mortality or recurrent IS as outcome measures, while our findings were mostly driven by death. Interestingly, GCA has been reported to be associated with a higher mortality in younger patients with neurocognitive deficits [24].

In our study, GCA remained significantly associated with our composite outcome also after adjusting for cSVD markers (CMB and WMH) and thus indicating its potential significance as a prognostic imaging measure in stroke patients with AF. Although our study does not allow to draw causal conclusion regarding the underlying mechanism, our results indicate that GCA may reflect both, vascular mechanism related to cSVD and neurodegeneration in these elderly subjects.

Moderate and severe GCA was associated with increased disability, including adjustment for age and baseline stroke severity based on the NIHSS, suggesting that cortical atrophy in AF patients indicates a higher risk of an unfavorable functional outcome after stroke. When adjusting for concomitant imaging markers of cSVD (CMB, WMH), this association was no longer significant. This is well in line with our previous study [12] where we found the presence of cSVD markers, especially the extent of WMH, to be associated with increased disability at the follow-up in AF-stroke patients. Overall, our findings suggest GCA potentially being an additional, easily assessable marker of an unfavorable outcome besides WMH.

Our study has some limitations: (i) GCA was analyzed using a visual rating scale, without detailed quantitative volumetric measurement of brain or cortical volume. However, we used an established scale, which was recently also applied in a similar study on the CROMIS cohort [20], and the scale allows easy and feasible assessment in a clinical setting; (ii) due to our sample size and especially the low number of ICH our analysis of the outcome events separately should be interpreted with caution; (iii) we did not control for other markers of cSVD such as enlarged PVS, lacunes, and microinfarcts; and finally (iv) the functional outcome after 3 months was assessed through telephone interviews, which may have influenced our results.

There are several strengths to our study: (i) our study is based on a prospective registry on stroke patients under OAC treated by experienced stroke experts at the referral stroke center and meeting current standard of care of AF-stroke patients. Thus, our cohort is likely to be a representative stroke cohort related to AF; (ii) all subjects underwent a comprehensive workup, including a standardized baseline clinical assessment, standardized MRI stroke protocol as well as repeated follow-up clinical examinations; (iii) MRI ratings were performed by three experienced investigators, blinded to treatment and outcome at the time of analysis. These readings were based on established scales and included consensus readings; (iv) besides ICH, we included IS and mortality as further clinically relevant outcome measures, thus extending previous studies; finally (v) in contrast to previous studies, our cohort included a high rate of subjects treated with DOACs [20, 25], which nowadays are considered the standard of care for nonvalvular AF.

Conclusions

In conclusion, GCA was associated with the composite outcome in our stroke patients treated with OAC for AF-related stroke. To the best of our knowledge, this is the first study examining the association of GCA on the risk of recurrent IS, ICH, and death in AF-related stroke patients under OAC. Our main findings stayed robust after adjusting for age and other imaging markers of cSVD. Further studies are necessary to evaluate the prognostic impact of GCA on stroke patients taking OAC for AF.

Statement of Ethics

The NOACISP-LONGTERM study protocol was reviewed and approved by the Local Ethics Committee named Ethikkommission Nordwest-und Zentralschweiz EKNZ, approval number BASEC PB_2016-00662, former EKBB 52/13. Written informed consent was obtained from all patients. Clinical Trial Registration: NCT 03826927.

Conflict of Interest Statement

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Marta Kubacka, Annaelle Zietz, Tolga Dittrich, Sabine Schaedlin, Alexandros Polymeris, Lisa Hert, Johanna Lieb, Benjamin Wagner, Joachim Fladt, Urs Fisch, David Seiffge, Valerian Altersberger, Philippe Lyrer, and Henrik Gensicke report no conflict of interest. Cristopher Traenka reports Travel Support from Bayer. Sebastian Thilemann has received travel grants from BMS/Pfizer. Stefan Engelter has received funding for travel or speaker honoraria from Bayer, Boehringer Ingelheim, and Daiichi-Sankyo. He has served on scientific advisory boards for Bayer, Boehringer Ingelheim, BMS/Pfizer, and MindMaze and on the editorial board of Stroke. His institutions have received an educational grant from Pfizer, compensation from Stago for educational efforts and research support from Daiichi-Sankyo, the Science

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Author Contributions

Marta Kubacka, Annaelle Zietz, Stefan Engelter, and Nils Peters contributed to the conception and design of the study. Marta Kubacka, Annaelle Zietz, Sabine Schaedlin, Lisa Hert, Johanna Lieb, Alexandros Polymeris, Benjamin Wagner, Valerian Altersberger, David Seiffge, Tolga Dittrich, Cristopher Traenka, Joachim Fladt, Urs Fisch, Sebastian Thilemann, Hendrik Gensicke, Gian Marco De Marchis, Leo Bonati, Philippe Lyrer, Stefan Engelter, and Nils contributed to the acquisition of data and/or critical revision of the manuscript. Marta Kubacka, Annaelle Zietz, Sabine Schaedlin, and Nils Peters contributed to analysis of data, drafting the manuscript, and preparing the figures. All authors contributed to revision of the manuscript.

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Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further enquiries can be directed to the corresponding author.

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